PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference MM/03048/PCT	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP 03/08448	International filing date *(day/month/year)* 29.07.2003	Priority date *(day/month/year)* 01.08.2002
International Patent Classification (IPC) or both national classification and IPC C07H17/08		
Applicant ZAMBON GROUP S.p.A. et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 1 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
01.03.2004	02.02.2005
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized Officer de Nooy, A Telephone No. +31 70 340-2338

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/08448

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-73 as originally filed

Claims, Numbers

1-32 as originally filed

Claims, Pages

75 received on 10.12.2004 with letter of 10.12.2004

2. With regard to the **language,** all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☒ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

   see separate sheet

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	21-29
	No:	Claims	1-20, 30-32
Inventive step (IS)	Yes:	Claims	21-29
	No:	Claims	1-20, 30-32
Industrial applicability (IA)	Yes:	Claims	1-32
	No:	Claims	

2. Citations and explanations

   see separate sheet

Re Item I

Basis of the report

The amendments filed with the letter of December 10, 2004 cannot be accepted since D1 (FR2735694) cannot be considered as an accidental disclosure. In D1 roxithromiycin free of the cladinose sugar is tested as anti-inflammatory agent. Thus, a disclaimer cannot be used to restore novelty over D1 (Article 19(2) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:
D1: FR2735694
D2: JP2001181294
D3: US5969161
D4: US3923784
D5: EP0682038
D6: US4743593

Novelty
The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-20, 30-32 is not new in the sense of Article 33(2) PCT.

The documents D1 (tables 1 and 2, roxithromycin without cladinose), D2 (page 34, structure II, pages 39, 41, 49, 57), D3 (column 5, structures VII and VIII), D4 (columns 5 and 6, structures III and IV) and D5 (page 4) disclose compounds falling within claims 1-19. Thus claims 1-19 lack novelty.
Document D6 (column 9, formula V) discloses compounds falling within claim 20. Thus, claim 20 lacks novelty.
Documents D1-D5 disclose above-mentioned compounds in pharmaceutical compositions, thus claim 30 lacks novelty.
Document D1 shows the use of roxithromycin without cladinose (tables 1 and 2) as antiinflammatory compound and for treating respiratory diseases. Thus, claims 31 and 32 lack novelty.

Inventive step

D1 presents the same solution to the same problem as in the present application, thus claims 1-3, 10-19, 30-32 lack an inventive step. However, when the applicant would be able to overcome the novelty objections mentioned above, an inventive step could be acknowledged for the following reasons:

The document D1 is regarded as being the closest prior art to the subject-matter of claims 1-32, and discloses roxithromycin without cladinose for use as antiinflammatory compound. It is found that cladinose is necessary for antiinflammatory activity (Tables 1 and 2).

The subject-matter of claims 1-32 therefore differs from this known subject matter in that antiinflammatory macrolides without cladinose are claimed.

The problem to be solved by the present invention may therefore be regarded as the provision of further antiinflammatory compounds.

The solution proposed in claims 1-32 of the present application would be considered as involving an inventive step (Article 33(3) PCT) if the novelty objections could be overcome for the following reasons:

Document D1 teaches away from the present invention in that cladinose is supposed to be partly or completely responsible for antiinflammatory activity (page 6, lines 36-38).

X is O, S, SO, SO_2 and NR_6, and R_6 is a hydrogen atom, a linear or branched C_1-C_3 alkyl, a C_1-C_3 alkoxycarbonyl group or a benzyloxycarbonyl group;
Y is a C_6H_4 group, a five- or six-membered heteroaryl ring having from one to three hetero atoms selected from nitrogen, oxygen and sulphur or is O, S, SO, SO_2 or NR_6 where R_6 has the meanings given above;
r is an integer from 1 to 3;
m is an integer from 1 to 6;
n is an integer from 0 to 2;
or R_1 forms a bond together with R_2;
R_2 is a hydrogen atom or forms a bond together with R_1;
R_3 is a hydroxy group or forms a group =N-O-R_5 together with R_4,
and R_5 is a hydrogen atom, a linear or branched C_1-C_5 alkyl, a benzyl optionally substituted with one or two substituents selected from nitro, hydroxy, carboxy, amino, linear or branched C_1-C_5 alkyl, C_1-C_4 alkoxycarbonyl groups, aminocarbonyl groups or cyano groups or a chain of formula

$$-(CH_2)r-X-(CH_2)m-Y-(CH_2)n-A$$

wherein
r, m, n, X, Y and A have the meanings given above;
R_4 is a hydrogen atom or forms a group =N-O-R_5 together with R_3,
and R_5 has the meanings given above;
and the pharmaceutically acceptable salts thereof,
~~provided, however, that R_1 is not a dimethylamino group when R_3 is hydroxy, and both R_2 and R_4 are a hydrogen atom.~~

2. A compound according to Claim 1, wherein the oxime group that may be present in position 9 is of E configuration.

3. A compound according to Claim 1, wherein R_1 is a hydrogen atom, an N-(C_1-C_3)alkyl-N-methylamino group, an N-(C_1-C_3)alkyl-N-

Provided, however, that
R_1 is not a dimethylamino group when R_3 is hydroxy, and both R_2 and R_4 are a hydrogen atom;
R_1 is not a dimethylamino group when in the substituent =N-O-R_5 in 9-position, R_5 is a hydrogen atom, a linear or branched C_1-C_5 alkyl, an unsubstituted benzyl group, or a chain $-(CH_2)_r-X-(CH_2)_m-Y-(CH_2)_n-A$ where r is 1, X is O, m is 2, Y is O, n is 1, and A is H;
R_1 is not a methylethylamino group when in the substituent =N-O-R_5 in 9-position, R_5 is a linear or branched C_1-C_5 alkyl or an unsubstituted benzyl group;